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Article (Accepted Version)

Rabe, Heike and Rojas-Anaya, Hector (2017) Inotropes for preterm babies during the transition period after birth: friend or foe? *ADC Fetal and Neonatal Edition*, 102 (6). pp. 547-550. ISSN 1359-2998

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Inotropes for preterm babies during the transition period after birth: friend or foe?

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Word count: 3014

Keywords: prematurity, transition after birth, inotropes, non-invasive biomarkers

Abstract

During the transition to extra-uterine life preterm infants are at high risk of developing circulatory failure. Currently hypotension is used as major diagnostic criteria for starting treatments such as fluid boluses, inotropes or steroids. Most of these treatment options have not been studied in large randomised controlled trials for efficacy and safety and are under discussions. A wide variety in their use is reported in the literature and clear evidence about which inotrope or other treatment should be preferred is lacking. In addition there is on-going debate about the appropriate threshold values for blood pressure. Other diagnostic measures for poor circulation are functional echocardiography, near-infrared spectroscopy, capillary refill time, base excess and serum lactate. Large randomised controlled trials for the use of dopamine and dobutamine in preterm infants < 32 weeks gestation are under way to fill the knowledge gaps on the assessment of circulatory compromise and on efficacy and safety of the studied age appropriate drug formulations.

Introduction

The first three days after birth represent a unique period in human life as the anatomy and dynamics of the circulatory system change for adaptation to extrauterine life. The foetal channels of open foramen ovale and patent ductus arteriosus normally close within the first day of life in term infants ,(1).

After clamping the umbilical cord, the first inflation breaths of the lungs and the associated increase in arterial oxygen content are accompanied by an increase in systematic vascular resistance resulting in increased afterload and a decrease in pulmonary vascular resistance leading to increased pulmonary blood flow. These haemodynamic changes are specific to the transition after birth and failure to adapt can lead to unique clinical challenges, (1).

Circulatory transition in preterm infants

Preterm infants born before 32 weeks gestation are at increased risk of failing to adapt to the circulatory changes after birth and thus will develop early haemodynamic insufficiency, (2, 3, 4). Compared to term infants myocytes are less well developed before 32 weeks gestation. Due to immature receptors the autonomic nervous system is less active and less responsive to stimuli in preterm infants. This leads to a reduced reserve of ventricular contractility of the heart which is less able to distend its ventricles thereby affecting the preload. An open ductus arteriosus often provides additional strain to the heart function through either bidirectional or left-to-right shunting. Preterm infants might be able to compensate for the increased preload through high systemic vascular resistance with normal blood pressure. However poor myocardial contractility can lead to low systemic blood flow and a decompensated stage at which hypotension might occur. About 80% of the infants who develop low systemic blood flow will subsequently develop systemic hypotension ,(5).

Challenges in diagnosing circulatory failure in preterm infants

In current clinical practice infants born at less than 32 weeks' gestation are routinely monitored for changes in vital parameters such as heart rate, systolic, mean and diastolic blood pressure and capillary refilling time ,(6, 7, 8, 9).

Challenges in blood pressure measurements

Preference is given to non-invasive methods of measuring blood pressure unless the infants have indwelling umbilical catheters so that it can be measured invasively. A prospective cohort study in 50 preterm infants of 24 to 32 weeks' gestation comparing non-invasive oscillometric blood pressure measurements with those obtained via indwelling arterial lines demonstrated a good relation between both methods during the first 24 h of life ,(10). However the first method cannot be used continuously, depends on the correct cuff size, it is problematic in very low birth weight infants and not as reliable as the second invasive method, (11,12). The traditionally used thresholds for blood pressure in preterm and term infants are based on studies done more than 3 decades ago, (13, 14). Attempts have been made to update these values with statistically defined normal values, (15, 16). Discussions are ongoing to decide whether these values describe a normal blood pressure range at which organ perfusion is maintained in particular for very low birth weight infants. The published reports vary with regard to investigating the relationship between low blood pressure, its treatments and long term neurodevelopmental outcome, (2, 5). A recent cohort study on 4907 preterm infants with a birth weight < 1500 g reported median values and interquartile ranges for the lowest mean arterial blood pressure during the first 14 h of life and by gestational age ,(17). The authors report that infants with blood pressure values below their median minimum blood pressure and who did not receive treatment with vasoactive medication had a higher incidence of intra-ventricular haemorrhage, broncho-pulmonary dysplasia or death.

Functional echocardiography

Due to the outlined problems with blood pressure other measures of cardiac function assessed by functional echocardiography using Doppler are being used to assess circulatory failure. Superior vena cava flow together with right and left ventricular output measurements have been used in preterm infants. Left ventricular output has been validated against the gold standard of determining cardiac outputs according to the Fick principle, using measured oxygen consumption calculated oxygen capacity, and oxygen saturation, in small cohorts of newborn infants and children ,(18, 19). In comparison to left and right ventricular output superior vena cava flow measured by echocardiography Doppler method is not influenced by the open foetal channels. It represents the portion of systemic blood flow from the upper body including the brain,

which is thought to be 70-80% in newborn infants ,(20). A study of 27 preterm infants showed a good correlation of superior vena cava flow with cerebral tissue oxygenation index used as a marker of cerebral blood flow and measured by near-infrared spectroscopy, (21). Several studies in preterm infants have demonstrated that low superior vena cava flow is associated with surrogate markers of poor outcome ,(22, 23, 24). Kluckow et al studied 126 babies born before 30 weeks' gestation of whom 48 (38%) had low superior vena cava (SVC) flow (< 41 ml/kg/min) within 24 hours of birth, ,(24). Fourteen infants (11%) developed significant intra-ventricular haemorrhage more than 6 hours after birth: 13/14 were in the low SVC flow group and 1/14 was in the normal SVC flow group. In another study Miletin et al studied 40 preterm infants, eight (20%) of whom had low SVC flow within 24 hours of birth ,(25). The incidence of a composite outcome of intra-ventricular haemorrhage and/or death was 4/8 (50%) among neonates with low superior cava flow and 2/32 (7%) among neonates with normal flow. Two recent studies have demonstrated an association between low superior vena cava flow and adverse outcomes using multivariate analysis: mortality ,(26) or severe ischemic events as an indication of impaired blood flow distribution ,(27). Based on the recent interest in echocardiography assessment in the early neonatal period guidelines and recommendation for training neonatologists in this bedside technique have been developed ,(28, 29).

Capillary refill time as a marker of circulatory perfusion

Other surrogate markers of circulatory perfusion failure described in the literature are capillary refill time and serum lactate.

Capillary refill time is used by clinicians as a proxy of cardiac output and systemic vascular resistance in newborn infants. The technique can be used at the bedside during normal clinical care but depends on variables such as skin site tested and pressure duration. Inter-observer variability can be wide and influencing factors might be ambient temperature, concomitant medications, and maturation-dependent skin blood flow regulation. There is a weak correlation between capillary refill time and markers of systemic perfusion both in the paediatric and in the neonatal population ,(9, 30). A capillary refill time of ≥ 3 sec had a sensitivity of 55% and specificity of 80% for low superior vena cava flow. A cut off for capillary refill time of ≥ 4 sec increased the

specificity to 96% but reduced the sensitivity to 29%. The area under the ROC was 0.72 (95% CI 0.64 to 0.8) ,(30).

Studies have been performed to combine biomarkers in order to better describe circulatory failure in newborn infants. When combining thresholds for mean blood pressure <30mmHg and/or capillary refill time ≥ 3 sec this had a similar diagnostic accuracy to a systolic blood pressure <40mmHg with 78% sensitivity, 63% specificity, positive predictive value 31% and negative predictive value 88% ,(30).

Serum lactate as a biomarker of tissue perfusion

Serum lactate as an additional biochemical marker of decreased tissue perfusion acidosis has not been systematically analysed in newborn infants. A study in ventilated infants found a poor correlation between base excess and blood lactate levels ,(31). More recently, a strong correlation between serum lactate and base excess has been reported in preterm infants in the transition period after birth. A single serum lactate above 5.6 mmol/L showed a high sensitivity and specificity to indicate adverse outcome in preterm infants on the first day of life ,(32). These studies did not include systematic evaluation of other haemodynamic parameters such as blood pressure, cardiac output or capillary refill time. Hypotensive infants who receive cardiovascular treatment with epinephrine have shown to increase their serum lactate levels despite normalising their blood pressure and improving their cerebral blood flow measured by near infrared spectroscopy (33, 34); this effect might be caused by increased gluconeogenesis and glucogenolysis due to epinephrine stimulation of the peripheral beta-2 receptors. A recent study of preterm infants observed an association of lactate > 4 mmol/L in the first 12 hours of life with the combined adverse outcome of death or severe brain injury ,(35).

Treatment options of circulatory failure

A few studies have measured plasma catecholamines in preterm and term babies during the first hours of life, (36, 37, 38, 39). Babies born after “normal” birth showed a rapid decline of catecholamine levels measured in umbilical arterial blood from immediately at delivery to 48 h after birth. All studies report lower plasma levels for premature infants due to the immature function of the adrenal glands.

Thus it seems reasonable to treat preterm infants with hypotension with inotropes such as dopamine, dobutamine, adrenaline or noradrenaline. They have been used since many years in spite of the immature receptors in preterm infants. Guidelines and recommendations for treatment pathways have been widely published and vary in their recommendations ,(40, 41, 42, 43). Discussions remain on which inotropes to use and whether their use is associated with increased morbidity and mortality ,(44). Dopamine and dobutamine have not been studied in large randomised controlled trials in preterm infants ,(44, 45).

Survey of inotrope use

In a recent large international survey on the diagnosis and management of hypotension in preterm infants Stranak et al ,(46) were able to collect data from 216 neonatal units around the world. More than 85% of centres use a fluid bolus of 10 ml/kg crystalloid solution as the first step to treat hypotension. Fifty-nine percent of centres would follow this up by a second fluid bolus and 14% by a third before starting inotropes. Dopamine as a first line treatment was used by 80% of the centres, of whom 18% combined it with dobutamine. There was great variation in the reported use for second line treatment such as dobutamine alone or in combination with dopamine, epinephrine, norepinephrine, steroids or milrinone.

Combining biomarker for drug efficacy assessments

The authors of the international survey were able to get data on preferred use of clinical and laboratory data used for the assessment of hypotension and poor perfusion in preterm infants ,(46). High priority was reported for capillary refill time, urine output, heart rate, peripheral skin colour, base excess and lactate values. Additional investigations for cardiac function were used to measure left and right cardiac output, fractional shortening of left ventricle and superior vena cava flow. A smaller proportion of neonatal centres used other additional assessment such as perfusion index, aEEG or near infra-red spectroscopy and relationship with neurodevelopmental outcomes ,(33, 34, 47, 48).

Extra placental blood influences postnatal circulatory adaptation

Delayed cord clamping enhances the transfer of placental blood to the baby at birth and 51% of the centres reported routine use in preterm infants. A Cochrane review ,(49) on the effects of delayed cord clamping in preterm infants reported benefits of higher blood pressure in the first days of life, less need for volume therapy or inotropes as short term outcomes and less need for blood transfusions. A recent meta-analysis for preterm infants < 30 weeks gestation and <1000 g birth weight confirmed these benefits for this very high risk group ,(50). Few studies on longer neurodevelopmental outcome have been published but significant harm of delayed cord clamping has not been identified yet ,(50). Milking (gentle stripping) of the umbilical cord towards the infant has been studied as an alternative method of providing extra placental blood in a short time to the infants. Two studies comparing delayed cord clamping of 30 or 60 seconds with 4 times milking of the cord in preterm infants < 32 weeks showed similar patterns for increasing blood pressure during the first week of life in both groups with very low need for inotrope treatment ,(51, 52). A neurodevelopmental follow-up study at 3.5 years corrected age showed no difference for both groups in the first comparison study ,(53). In January 2017 the large Australian Placental transfusion Study has completed enrolling more than 1600 preterm infants into a randomized controlled trial of comparing immediate with delayed cord clamping of more than 60 seconds, (54). The data from this study will significantly enhance the knowledge on this simple intervention.

The need for clinical studies

The need for large clinical studies on the use of dopamine and dobutamine has been prioritized by the European Commission and the European Medicines Agency and therefore funding was made available under the Seventh Framework Programme for Health.

The HIP trial

The HIP consortium ,(55) is currently studying an age appropriate formulation of dopamine in preterm infants from 23 weeks to 27 weeks and 6 days gestational age during the first 72 hours of life, (44). Infants can be enrolled into a randomised controlled trial if they meet the inclusion criteria with a mean blood pressure

measured by indwelling arterial line of 1 mmHg or more below a mean blood pressure value equivalent to the gestational age in weeks. Infants with intra-ventricular haemorrhage grade III or IV on cerebral ultrasound, life threatening congenital abnormalities or who are classed as non-viable are excluded. Infants will be randomised to receive a fluid bolus of 10 ml/kg of normal saline followed by either Dopamine started at 5 µg/kg/min with a maximum dose increase up to 20 µg/kg/min or normal saline as placebo in an equivalent amount of infusion volume. In addition thresholds for capillary refill time > 4 s and lactate > 4 mmol/L will be used to assess the need for further inotrope treatment as per local guidelines. Subgroups of infants will be assessed for evaluation of end-organ perfusion by measuring cardiac output (right and left ventricular output, superior vena cava flow). Near-infrared spectroscopy will be used to measure cerebral oxygenation and continuous multi-channel EEG to study the effects of mean blood pressure changes on cerebral electrical activity in selected centres. Primary outcome measures are survival without significant brain injury at 36 weeks' postmenstrual age and survival without neurodevelopmental disability at 2 years of age corrected for prematurity ,(44).

The NEO-CIRC trials

The NEO-CIRC consortium ,(56, personal communication) has taken a similar approach to study an age appropriate formulation of dobutamine. After completion of a pilot exploratory study (unpublished data) the consortium is currently setting up a randomised controlled trial similar to the HIP-Trial in preterm infants between 24 and 32 weeks gestation who develop signs of circulatory failure during the first 72 h after birth. It is hoped that by the end of both studies the international community will be able to develop a new consensus on the definition of neonatal circulatory failure for preterm infants in the transition period after birth. The studies will hopefully contribute to the availability of age appropriate licensed inotropes for this age group.

Recommendations for research

An international consensus on a definition of circulatory failure in the transition period is urgently required. Large randomised controlled trials are under way to provide evidence on efficacy and safety of dopamine and dobutamine in the treatment of hypotension of preterm infants. Future studies in this field should take other measures than blood pressure alone and surrogate biomarkers for tissue perfusion

such as functional echocardiography, capillary refill time, base excess and lactate levels into account. Enhanced placental transfusion at birth either by delayed cord clamping or milking of the cord can be the start of preventative measures of hypotension. Information about its use should be recorded in all future studies. An international agreement about valid thresholds for treating low or high blood pressure in the newborn period is urgently required. The Haemodynamics Working Group of the International Neonatal Consortium hosted by the Critical Path Institute is currently working on a consensus, (57).

Acknowledgement

The authors thank Igor Brbre, clinical librarian, for his help with the literature searches. We thank the partners of the NEOCIRCULATION consortium (*Chief Investigator: Adelina Pellicer, Madrid, Spain. Principal Project Co-ordinator: Heike Rabe, Brighton, UK. Local Investigators: Philip Amess, Neil Aiton, David Crook, Ramon Fernandez, Liam Mahoney, Heike Rabe, Hector Rojas-Anaya, Brighton, UK; Vincent Jullien, Thomas Le Saux, Gerald Pons, Sarah Zohar, Paris, France; Frank Biertz, Marjan Brinkhaus, Armin Koch, Yvonne Ziert, Hannover, Germany; Jon Lopez Heredia, Victoria Mielgo, Adolf Valls-i-Soler, Bizkaia, Spain; Wolfgang Göpel, Christoph Härtel, Lübeck, Germany; Charalampos Kotidis, Mark Turner, Michael Weindling, Liverpool, UK; Claudia Roll, Datteln, Germany; Maria del Carmen Bravo, Fernando Cabañas, Marta Pavia Madrid, Spain; Clare Gleeson, Simon Bryson, Cheshire, UK; Gabriela Zaharie, Cluj-Napoca, Romania; Géza Bokodi, Miklós Szabó, Budapest, Hungary; Tibor Ertl, Simone Funke, Pécs, Hungary; Ebru Ergenekon, Kivilcim Gücüyener, Şebnem Soysal, Ankara, Turkey; Olaf Dammann, Christiane Dammann, Boston, US.*

Neo-Circulation Expert Advisory Board: Tonse N. K. Raju, Bethesda, USA; Nicholas Evans, Sydney, Australia; Stephanie Läer, Düsseldorf, Germany; Silke Mader,

Karlsfeld, Germany; Monika Seibert-Grafe, Mainz, Germany, Adrian Toma, Bucharest, Romania.

Neo-Circulation Data Monitoring Committee: Gorm Greisen, Copenhagen, Denmark; Lena Hellström-Westas, Uppsala, Sweden; Josef Högel, Ulm, Germany.) for their ongoing scientific discussions of the topic.

Contributors

HR and HRA prepared the manuscript.

Funding

HR and HRA are supported by the grant agreement FP7-HEALTH-282533 NEO-CIRC

Competing interests: none declared

Provenance and peer review: Commissioned; externally peer reviewed.

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